REMARKS

Claims 28, 29, 31-48, 55-58, and 62 are pending in the application and have been examined. Claims 28, 29, 31-48, 55-58, and 62 stand rejected. Claims 33, 35, 48, and 56 have been canceled in this response. Claims 28, 29, 34, 41, 44, 45, and 55 have been amended in this response. Claims 63-66 have been added in this response. Applicant respectfully requests reconsideration and allowance of Claims 28, 29, 31, 32, 34, 36-47, 55, 57, 58, 62, and 63-66.

The Rejection of Claims Under 35 U.S.C.§ 112, Second Paragraph

Claims 41, 44, 45, and 48 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to set forth the subject matter which applicant regards as the invention. Claim 48 has been canceled. Claim 41 has been amended to correct a typographical error related to its dependency. Claim 44 has been amended to provide proper antecedent basis for the phrase "the virus." Claim 45 has been amended to correct a typographical error by removing the term "viral" from the phrase "viral vector." Withdrawal of this ground for rejection is respectfully requested.

The Rejection of Claims Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 28, 29, 31-48, 55-58, and 62 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking an enabling description in the Specification. The Examiner alleges lack of enablement with respect to: (1) treatment of any disease or disorder of the inner ear linked with damage or destruction of the sensory cells by administering an inhibitor of any cell cycle inhibitor present in the inner ear; (2) administration of any active ingredient able to inhibit the action of any cell cycle inhibitor in the inner ear; and (3) methods of systemic administration of a broad range of compounds. Applicant respectfully disagrees with the Examiner's conclusions for the following reasons.

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As an initial matter, applicant wishes to point out that Claim 48 has been canceled, and independent Claims 28, 29, and 55 have been amended to clarify the invention. Claim 28 has been amended to recite "a process for the treatment of perception deafness, comprising the step of locally administering an active ingredient to the inner ear that at least partly inhibits or eliminates the action of at least one cyclin-dependent kinase inhibitor present in the inner ear selected from the group consisting of $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$." Claim 29 has been amended to recite "a method of treating a mammalian subject suffering from perception deafness, comprising locally administering an active ingredient to the inner ear that at least partly inhibits or eliminates the action of at least one cyclin-dependent kinase inhibitor present in the inner ear selected from the group consisting of $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$." Claim 55 is directed to a pharmaceutical composition comprising at least one active ingredient able to inhibit at least one cyclin-dependent kinase inhibitor present in the inner ear selected from the group consisting of $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$.

Applicant submits that the invention as claimed in Claims 28, 29, and 55 is enabled by the application as filed in view of the knowledge of one skilled in the art at the time of filing. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in a patent coupled with information known in the art without undue experimentation. With respect to what constitutes undue experimentation, the following factors are relevant: the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the amount of guidance presented, the presence or working examples and the quantity of experimentation necessary. (*In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (stating, "the key word is 'undue,' not experimentation'").

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A. The Specification provides specific guidance on the treatment of perception deafness by inhibiting cell cycle inhibitors $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$.

According to the Examiner, the Specification does not provide any guidance on what specific diseases or disorders can be treated or what specific cell cycle inhibitor can be targeted for inhibition. Applicant notes that the claimed invention is directed to treatment of perception deafness and submits that the Specification provides specific guidance on how to make and use the claimed invention. The Specification defines perceptive deafness as partial or complete loss of the power of hearing which can be attributed to damage or destruction of the sensory cells of the inner ear (see Specification, page 1, lines 13-18). The Specification further provides that regeneration of the hair sensory cells participating in acoustic transduction in the inner ear is a treatment for perceptive deafness (see Specification, page 4, lines 3-6). The use of inhibitors of cyclin-dependent kinase inhibitors of the KIP/CIP family, specifically, $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$ as active ingredients to initiate or stimulate the regeneration of hair sensory cells is described throughout the Specification (see, e.g., Specification at page 4, lines 4-25, page 7, lines 25-30, and the example on page 8, lines 15-37, to page 9, lines 1-27). Moreover, as noted by the Examiner, experimental evidence is provided in the working example of the Specification demonstrating that genetic deletion of $p27^{Kip1}$ results in ongoing proliferation of sensory hair cells (see Specification at page 8, lines 15-37, to page 9, lines 1-27). Further, in $p27^{Kip1}$ heterozygous mice, new hair cell production can be stimulated by otoxic injury to the cochlea. These results indicate that cellular regeneration in supporting cells in the inner ear is blocked by $p27^{Kip1}$, a member of the KIP/CIP family, and inhibition of the function of $p27^{Kip1}$ results in supporting cell proliferation and hair cell differentiation. Therefore, applicant submits that the Specification provides adequate guidance on treatment of perception deafness by inhibition of at least one of $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$.

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B. The Specification provides specific guidance on use of the claimed class of inhibitors of $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$ in view of the state of the art at time of filing.

According to the Examiner, the Specification does not provide any guidance on administration of any active ingredient for the inhibition of any cell cycle inhibitor present in the inner ear. As an initial matter, applicant notes that the invention as claimed in Claims 28, 29, and 55 is directed to active ingredients that inhibit the KIP/CIP family of cyclin dependent cell cycle inhibitors, specifically, $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$. Applicant submits that the Specification provides sufficient guidance in view of the state of the art to enable the claimed invention. As stated by the court in *Enzo Biochem. Inc. v. Calgene*, "[i]t is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed." 188 F.3d at 1374, 52 U.S.P.Q.2d at 1138 (Fed. Cir. 1999).

Applicant submits that the Specification contains specific guidance for the use of peptides and proteins as active ingredients that inhibit the KIP/CIP family of cyclin dependent cell cycle inhibitors (see Specification at page 4, lines 36-41, to page 5, line 1). The Specification describes the identification of specific high affinity bonding points at which peptide-peptide interactions occur between the $p27^{Kip1}$ and the CDK2 or cyclin A. See Specification at page 5, lines 32-36. Further, a peptide structure optimized for use as an active ingredient is described in the Specification which bonds with high affinity at the point of interaction with cyclin A or CDK2, preferably a peptide up to 15 amino acids which can be introduced directly or expressed using a recombinant gene (see Specification page 6, lines 5-12).

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Applicant submits the Specification is also enabling with respect to $p21^{Kip}$ and $p57^{Kip2}$ in view of the state of the art which teaches that "members of the KIP/CIP family contain a 65 amino acid region with homology (38%-44% identity) at their N-terminal portions, which is necessary and sufficient to bind to and inhibit cyclin-dependent kinase complexes (Russo et al., *Nature 382*:325-331, 1996, attached hereto as Attachment A; see also U.S. Patent No. 5,688,665).

The Examiner has relied on Agrawal et al., *Molecular Medicine Today 6:*72-81, 2000; Branch, *Trends in Biochemical Sciences 23*:45-50, Feb. 1998; Green et al., *J. Am. Coll. Surg. 191*(1):93-105, 2000; and Jen et al., *Stem Cells 18*:307-319, 2000, to conclude that the therapeutic *in vivo* use of antisense oligonucleotides is a highly unpredictable art. Specifically, the Examiner has cited a statement in Jen et al. that "[o]ne of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery.... Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable." As an initial matter, applicant points out that the claimed invention is directed to localized delivery to the inner ear, thus avoiding the problems associated with systemic delivery discussed in Jen et al. Further, applicant respectfully points out that nonantisense effects the Examiner refers to, as discussed in Branch, are often therapeutically useful for boosting the efficacy of immunotherapies and vaccines (see Branch, page 46, first column). Therefore, applicant submits that the approach of using local delivery of antisense oligonucleotides to the inner ear allows for efficient and therapeutic delivery of antisense compounds.

The Specification and the Declaration of Dr. Jonathan Kil, provided in response to Paper No. 10, provide specific guidance with respect to effective antisense molecules that are useful in the practice of the invention as well as appropriate concentrations effective to produce a

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therapeutic result. The Specification describes the use of antisense nucleic acid molecules including DNA and RNA which can be introduced *in vivo* with the aid of lipid compounds (see Specification, page 5, lines 11-23). Further, the Specification describes that very low concentrations of inhibitor, such as, for example, approximately 10nM/l can suffice for performance of the invention (see Specification, page 6, lines 21-29). As previously described in response to Paper No. 10, the Kil Declaration further describes the local delivery of specific antisense oligonucleotides to the inner ear, resulting in inhibition of $p27^{Kip1}$ mRNA and protein levels. Applicant notes the use of 15mer p27Kip1 SPI5101 was known in the art at the time of filing (see Coats et al., *Science 272*:877-880, 1996).

C. The Specification provides specific guidance that enables the method of local administration to the inner ear in view of the state of the art at time of filing.

The Examiner states that the specification provides no guidance related to how to administer an inhibitor to a subject. Applicant submits that the claimed invention, directed to local administration of an inhibitor of at least one of $p21^{Cip1}$, $p27^{Kip1}$ or $p57^{Kip2}$ to the inner ear, is enabled by the Specification in view of the state of the art at time of filing.

The Specification provides on page 7, lines 9-22:

> [t]he target location of the process according to the invention, namely the inner ear, is particularly suitable for local application. Thus, in the present case the active ingredient can be introduced into the so-called perilymphatic space of the inner ear of the mammal, particularly human. This is a small liquid space with a very slow exchange rate, which is accessible to therapeutic intervention from the middle ear, e.g., via the membrane of the circular window. This perilymphatic space has a volume of only approximately 20 microliters and is also in direct contact with the cells of the corti-organ. This ensures a direct action of the active ingredient on the sensory epithelium with its hair cells and supporting cells.

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Further, the Examiner acknowledges that the Kil Declaration, provided in response to Paper No. 10, demonstrates inhibition of a cell cycle inhibitor using antisense delivered locally to the ear (see Paper No. 13, page 12).

For all the reasons provided above, applicant submits that the invention of Claims 28, 29, and 55 is supported by an enabling description in the Specification. The quantity of experimentation required for one skilled in the art to practice the invention would not be undue in view of the scope of the claims, the state of the prior art, the high level of skill of those in the art and the specific guidance provided in the Specification. Accordingly, applicant respectfully requests removal of this ground of rejection.

The Rejection of Claims Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 28, 29, 31-48, 55-58, and 62 have been rejected under 35 U.S.C. § 112, first paragraph as containing subject matter that allegedly lacks an adequate written description in the Specification. The Examiner has taken the position that the Specification does not provide a detailed chemical structure or common structural characteristics of the active ingredients, such that one of skill in the art would recognize that the inventor was in possession of the broad genus of active ingredients claimed at the time the application was filed.

As stated in the PTO Guidelines, 66 Fed. Reg. at 1106, the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics which coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *See also Enzo Biochem. Inc. v. Gen-Probe Inc.,* 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002) (stating that written description requirement may be met by disclosure of functional characteristics when coupled with a known or disclosed correlation between function and structure.)

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Applicant wishes to point out that the structure of the pending claimed compounds does correlate with function. Applicant notes that the pending claims are limited to inhibitors of the KIP/CIP class of inhibitors. The genus of the KIP/CIP family of claimed inhibitors is described in the Specification (see, e.g., Specification at page 4, lines 4-25). Specifically mentioned are three members of the class, $p21^{Cip1}$, $p27^{Kip1}$, and $p57^{Kip2}$. One of ordinary skill in the art at the time of filing would know that these three cyclin-dependent kinase inhibitors are highly related with respect to structure and function (see e.g., Russo et al., *Nature 382*:325-330, 1996, attached hereto as Attachment A). Russo et al. describes the sequence and functional similarities of the KIP/CIP family of cyclin-dependent kinase inhibitors, including $p27^{Kip1}$, $p21^{Cip1}$ and $p57^{Kip2}$, which all contain a 65 amino-acid region with 38%-44% identity at their N-terminal portions, which is necessary and sufficient to bind to and inhibit cyclin-CDK complexes (see Russo, page 325, first column). With respect to particular embodiments of the active ingredient, the structure of $p27^{Kip1}$, $p21^{Cip1}$ and $p57^{Kip2}$ were all known in the art at the time of filing (see Polyak et al., *Cell 78*:59-66, 1994, attached hereto as Attachment B; Nakanishi et al., *EMBO J. 14*(3):555-63, 1995, an abstract of which is attached hereto as Attachment C; and Lee et al., *Genes & Development 9*:639-649, 1995, attached hereto as Attachment D).

Moreover, inhibitors of the KIP/CIP family were known at the time of filing (see Coats et al., *Science 272*:877-880, 1996 provided in applicants' response mailed March 7, 2003; Hauser et al., *Cell Growth and Differentiation 8*:203-211, 1997, cited by the Examiner in the previous Office Action, Paper No. 10; U.S. Patent No. 5,688,665, attached hereto as Attachment E, and Freemerman et al., *Leukemia* 11: 504-13, attached hereto as Attachment F). The specification provides a written description of inhibitors of KIP/CIP inhibitors in the form of proteins or peptides (see e.g., Specification at page 4, lines 36-41, page 5, lines 32-41 and page 6, lines 5-21), nucleic acid molecules (see e.g., Specification at page 5, lines 2-10, page 6, lines 33-

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35) including antisense DNA (see e.g., Specification at page 5, lines 11-23) as well as viral and non-viral vector delivery (see e.g., Specification at page 6, lines 35-42 and page 7, lines 1-5). Therefore, applicant submits that the written description requirement of pending Claims 28 and 29 is met in view of the disclosure in the Specification of functional characteristic inhibitors of $p27^{Kip1}$ share, which allow for regeneration of hair cells, coupled with the knowledge in the art that $p27^{Kip1}$ belongs to the family of inhibitors that share highly similar structure.

The Examiner has further stated that the written description requirement of Claims 55 and 56 has not been met because Claims 55 and 56 are directed to compositions that encompass nucleic acids and amino acids. Applicant notes that Claim 56 has been canceled. With respect to Claim 55, applicant submits that the disclosure of functional characteristics of the KIP/CIP family coupled with the known correlation between structure and function, as described *supra*, satisfies the written description according to *Enzo Biochem. Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609. Applicant submits that Claim 55 is directed to a composition containing a defined class of active ingredients which were sufficiently described in the Specification and known in the art at the time of the invention. As described *supra*, the nucleic acid and amino acid sequences of the inhibitors $p27^{Kip1}$, $p21^{Cip1}$ and $p57^{Kip2}$ were known in the art and therefore one of skill in the art would have possession of this information at the time of filing. Therefore, applicant respectfully requests withdrawal of this ground of rejection.

The Rejection of Claims Under 35 U.S.C. § 102(b)

Claims 55 and 56 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Hauser et al., *Cell Growth and Differentiation 8*:203-11, 1997. Applicant notes that Claim 56 has been canceled. According to the Examiner, Hauser discloses nucleic acids inhibitors of cell cycle inhibitors, including antisense targeted to $p27^{Kip1}$ in a solution comprising a pharmaceutically acceptable carrier. Applicant respectfully submits that the solution disclosed in

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Hauser et al. (comprising water, KBM media, and antisense DNA) is not anticipatory because the composition of KBM media is not disclosed in Hauser, nor is the composition of KBM media provided by Clonetics and therefore not an enabling reference. See Clonetics product information sheet for KBM media, accessed via http://www.cambrexbioproductseurope.com/cloneticskeratinocytemedia.pdf, (last visited on 10/29/03) attached hereto as Attachment G. Further, the KBM media disclosed in Hauser is not a pharmaceutically acceptable carrier for *in vivo* therapeutic delivery as claimed in the invention, because KBM media is "not intended or approved for human or veterinary use, for application to humans or animals, or for use in *in vitro* diagnostic or clinical procedures." See Attachment F. Therefore, Hauser et al. does not disclose or suggest every limitation of the invention claimed in Claim 55 and does not anticipate these claims. Accordingly, applicant respectfully requests withdrawal of this ground of rejection.

New Claims 63-66

New Claims 63-66 are directed to a process for promoting regeneration and growth of sensory hair cells in the inner ear of a mammalian subject, using the methods as described for Claim 28. No new matter has been introduced. Support for Claims 63-66 can be found in the Specification as filed, for example, at page 4, lines 3-6, and page 8, lines 15-37, to page 9, lines 1-27.

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CONCLUSION

In view of the above amendments and the foregoing remarks, applicant respectfully submits that all the pending claims are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicant's attorney.

Respectfully submitted,

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